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ABSTRACT

COVID 19 is one of the most severe infectious diseases in human history because of its world-wide pandemic, rapid spreading, high mortality and lack of effective vaccine, and therefore the studies on herd immunity for COVID 19 are needed urgently. Natural infection, vaccination and artificial small-amount pathogen infection (ASAPI) are three potential strategies for establishing herd immunity against COVID 19. The features and feasibility of these strategies are discussed in this review.

KEYWORDS: COVID 19, SARS-CoV-2, Virus, herd immunity, infectious diseases, epidemic, pandemic, infection, vaccination.

INTRODUCTION

COVID 19 is a respiratory infectious disease, caused by the recently named virus SARS-CoV-2.^[1,2] It has led to more than 300,000 deaths worldwide and its case number is still increasing.^[3] As the virus pandemic spreads throughout the world, herd immunity^[4,5] may be a way to reduce virus spread and its life threat. This has been initially practiced in some European countries,^[4] such as Italy, Spain, UK and Sweden.

Herd immunity, a type of immune barrier,^[4,5] can be reached when over 70% (at least 60%) of the population acquires the effective immunity to pathogenic bacteria or viruses,^[6] and once it is established, the disease has little chance of becoming epidemic or pandemic. The three ways to establish the herd immunity are natural infection, vaccination and artificial small-amount pathogen infection.

Natural infection is the easiest way for a population to acquire herd immunity but would result in the deaths of COVID 19 patients with higher mortality. With this disease, the mortality rates vary from 0.3-12% in different countries, cities or localities.^[7-10] If we take the figure 12%, natural infection is definitely not ideal for acquiring herd immunity. However, because the actual infected population could be up to 30 folds more than that of the clinical patients reported in recent epidemic investigations,^[11-14] the real mortality could be less than 1%. Thus, natural infection could still be a probable strategy for attaining herd immunity, especially when a vaccine is not yet available. To ascertain the immunity level of a population, a large-scale epidemic

investigation that includes detection of antigen specific IgM/IgG antibodies^[15-19] for the current level of natural infection is critical for determining if natural infection can be planned for the herd immunity against COVID 19.

In addition to the protective antibody level in a population, whether SARS-CoV-2 infected people could really attain immunity to future SARS-CoV-2 virus infection is unconfirmed at present.^[2,4,7] This issue would be further complicated with the possible antigen shift of the virus spike protein, although it is currently believed to be conservative. Therefore, the strategy of natural infection for the establishment of herd immunity could be very risky without knowing the immune efficacy of the virus infection. Once it is proofed that the natural infection can induce adequate protective immunity to SARS-CoV-2 virus, we can move forward to the next step: to determine the suitable way to reduce the severity of infection by protecting people from infecting the large amount of the virus. In our animal studies^[20-24] on Influenza for primarily determining the relationship between virus amount and the infection severity, we found the virus dose at 1xLD⁵⁰ (50% Lethal Dose) could be more than 320-fold higher than the 50% minimum infection dose (MID⁵⁰) with which the 50% mice just got some mild symptoms (fever and cough), and 2560-fold higher than the minimum dose to stimulate immunity (SIMD) with which the mice are positive for antigen specific-IgG antibody and all animals can be protected from death with the virus challenge at 1xLD⁵⁰. This indicates that the severity of the disease in the infected individual depends on the amount of the virus present in the individual's body, and the difference between MID⁵⁰

and SIMD allows the infected individuals to have inapparent infection but get immunized. Clearly, it would be ideal that a person only experiences an inapparent or subclinical infection but acquires immunity to the virus by only infecting a small amount of virus. Similar to influenza, a large portion of inapparent/subclinical SARS-CoV-2 virus infection also exists in the population,^[1,2,25,26] which makes the herd immunity possible by reducing the viral load in natural infection. Some protection measures, such as washing hands properly, wearing masks, gloves, goggles and maintaining social distance in public, can significantly reduce the virus spread and should be emphasized in the process of establishing herd immunity to minimize the risks of severe disease and death in establishment of herd immunity with natural infection. For the same reason, anti-virus medicine should also be applied as some drugs have been demonstrated effective in COVID 19 treatment.^[5,27-30] The clinical application of any medicine that can inhibit virus propagation at the early stage of the infection would be greatly helpful to reduce the severity of the disease and increase the safety and likelihood of herd immunity establishment by natural infection. Because the elderly,^[20,31] immunocompromised and the people with preexisting conditions (such as diabetes and hypertension), have much higher risk of the death due to respiratory infection including COVID 19,^[32,33] they should not be included in the population considered to establish herd immunity by natural infection.

Vaccination would be an ideal way for both individual protection and herd immunity. Currently, many COVID 19 vaccines are in development and some already in clinical trials.^[2,34-36] Among these vaccines, RNA vaccine, inactive vaccine and genetic recombinant vaccine are in clinical trials and DNA Vaccine, spike protein vaccine, subunit vaccine and peptide vaccine are also approaching clinical trial.^[2] However, given the failure in the development of other coronavirus vaccines, such as SARS, MERS and Ebola vaccines,^[2,34] the development of a COVID 19 vaccine may face similar problems. For the reasons that are unclear, individuals immunized with these vaccines could have more severe diseases when they are infected with the respective virus.^[35-38] Some assumptions regarding this phenomenon include tissue damages caused by cellular immunopathology,^[36-38] and/or antibody-dependent enhancement (AED)^[35,36] in which the antibodies induced by the vaccine mediate the virus's entry into cells. In our studies on the influenza DNA vaccine,^[39] we found that the stronger cellular immune response accelerated the clearance of influenza virus and the recovery of the mice infected with smaller amount of virus. However, we also found that the mice immunized with NP and HA DNA vaccines and exhibited a higher cellular immune response had higher mortality (19/20) than the control (11/20, $P < 0.05$) in the high dose (1.5xLD₅₀) virus-challenged mice, whereas when the cellular immune response was partially blocked in vivo by antibodies against the NP antigen, the mortality was reversed, 3/20

and 12/20, respectively ($P < 0.01$). In contrast, in the low dose (1xLD₅₀) virus-challenged mice, all 20 immunized mice survived, but 9/20 in the control group died ($P < 0.01$). This suggested that the excessive cellular immune response could be harmful for the individuals infected with a large amount of virus, and could be a possible reason for the more severe disease in vaccine clinical trials in certain situations. Coronavirus vaccines might have the same problem. Because some peptides in the vaccine antigen protein may tend to overwhelmingly induce a cellular immune response rather than a humoral one, genetic modification of the genes coding those peptides or simply blocking the cellular immune response for those patients with rapidly progressing illness would be preferable. In addition, although vaccines are currently being rapidly developed for COVID 19, it is almost impossible to affect the first wave of the pandemic because the development may take a year or longer.^[31]

Because both natural infection and vaccination are facing major hurdles in establishing herd immunity against COVID 19, artificial small-amount pathogen infection (ASAPI) might be a more promising strategy to protect the population from the epidemic. The application of ASAPI in establishing herd immunity is based on the known amount of virus causing only inapparent SARS-CoV-2 virus infection. The advantages of ASAPI are the following: (1) it requires neither developing a new vaccine nor evaluating the efficacy and side effects of a new vaccine; (2) it does not cause severe disease because the controlled amount of the virus used in ASAPI only causes inapparent/subclinical virus infection, which is definitely less severe than most natural infections; and (3) the effects of virus antigen changes caused by the virus gene mutation on the immune capacity of ASAPI are minimal compared with those in natural infection and vaccination. The reason for the latter is that the only requirement for ASAPI to match the new antigen is a simple virus processing procedure involving the isolation, identification, amplification, and purification of the newly mutated virus, while this would be much more complicated and difficult in case of natural infection and vaccination and would almost require to repetition of the entire procedure.

Although ASAPI has many advantages over natural infection and vaccination in establishing herd immunity, it has many prerequisites for its application. First, it must be ensured that there is no significant portion of chronic SARS-CoV-2 virus infection following the initial infection. This can be simply determined by an epidemic investigation that includes examination of the virus-specific IgM antibody and virus RNA in the blood of recovered patients. Second, the virus infection must create effective immune protection. This can also be determined by epidemic investigation on the re-infection rate of patients who recovered from the first infection and then came in contact with the patients with active SARS-CoV-2 infections. Third, the difference between

the smallest amount of the virus that can stimulate effective immunity (similar to SIMD) and the amount that causes severe disease is large enough for the recipients to get immunized but not contract a severe disease. Ideally, that the difference between the minimum amount of the virus that can stimulate effective immunity and the minimum amount that causes apparent infection is greater than 100-fold. If not, repeated lower dose of ASAPI should be considered for establishing effective herd immunity. Fourth, the safety of the research, preparation, transportation, preservation of the virus must be ensured by following restrictive protocols, thus, requiring all individuals working on ASAPI receive proper training. Fifth, if people can be immunized by inoculating ASAPI through non-respiratory routes, (e.g. intracutaneous, subcutaneous, or intramuscular), the virus can be served as a vaccine directly and quarantine of the ASAPI receivers may not be needed. Otherwise, if effective immunity can be acquired only by the virus inoculation through the respiratory tract, a restrictive quarantine plan for each ASAPI receiver must be prepared and implemented to prevent the possible spread of the virus. Sixth, it would be desired to establish an *in vitro* model or/and an animal model to determine the proper dose for ASAPI by testing the virulence of the virus.

Quarantine is important for both natural infection and ASAPI in successful establishment of herd immunity to COVID 19. In one of our experiments, when we separated Influenza virus-infected mice and uninfected mice with two layers (5 mm apart) of screen with different apertures at 1.999 (Mesh10), 0.97(Mesh20), 0.318(Mesh 50) or 0.074mm (mesh 200), 10 days after the mice in infection group were infected with Influenza virus at $10 \times \text{MID}^{50}$, we examined the infection of the uninfected mice with quantitative rtPCR for nasal wash virus RNA and ELISA for serum antigen-specific IgM/IgG, we found that all animals in un-infection groups got infected but those in the cages with mesh 200, and the virus shedding amount of the originally uninfected mice correlated to the pore size of the screen ($R^2=0.92$, $P<0.0001$). It suggested that all types of masks used in human protection, no matter what materials they are made with or if they are N95, can reduce the virus infection to a certain extent. This is very important for the safety in establishing herd immunity to COVID 19 with natural infection and ASAPI, especially for the people who do not have commercial masks. Another interesting result from our preliminary experiment for testing LD^{50} of influenza virus-infected mice is that the mice in the condition of one mouse per cage had significantly lower mortality than that of 4 mice per cage, suggesting that the infected mice could be further reinfected by other infected mice, and the repeated infections from each other resulted in exacerbation of their disease. Therefore, all infected people should be separated and properly quarantined to avoid uncontrolled infection in the establishment of herd

immunity to COVID 19 with natural infection and ASAPI.

In summary, as more medicines^[40] are demonstrated effective for inhibiting SARS-CoV-2 virus at disease early stage, it would be safer and more feasible to use natural infection to establish the herd immunity to the virus infection. Before availability of an effective vaccine, ASAPI has always been a potential strategy for the population to acquire herd immunity.

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